Remarks

Claims 1-17 and 28-37 are pending and rejected in this application. Applicant believes that the claims, as pending, are clearly distinguishable over all of the references on record. Reconsideration in light of the arguments below, and allowance of these claims, is therefore requested.

Restriction Requirement

Applicant acknowledges that the Response filed September 30, 2003, is being treated as an election without traverse.

Information Disclosure Statement

The current Action states that the information disclosure statement (IDS) filed April 14, 2003, "fails to comply with 37 C.F.R. §1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office." Because of the alleged defect, "it [the IDS] has been placed in the application file, but the information referred to therein has **not** been considered" (emphasis in original).

Applicant's representative has been unable to reach the Examiner to discuss the alleged defect with this IDS. It appears, however, that the Examiner is stating that the Office file does not contain a copy of the Form 1449, which lists the patents, publications, and other information submitted with the April 14, 2003, IDS. Applicant therefore submits herewith, as **Exhibit A**, a copy of the IDS documents that were mailed on April 11, 2003, and acknowledged by the Office on April 14, 2003. Included in Exhibit A are: a transmittal page, a one page Statement, and a two page Form 1449, which lists the 20 references that were submitted with the IDS. Also submitted herewith as **Exhibit B** is a copy of the postcard that accompanied the IDS, and a copy of the returned postcard, showing the Office acknowledgement stamp, dated April 14, 2004. The postcard clearly lists that the IDS filing included the form PTO 1449 and 20 references.

It is believed that provision of Exhibits A and B overcomes this objection, and that the Examiner can now consider and acknowledge the information provided with the April 14, 2003, IDS. However, if the file is also missing the 20 references that were provided with that IDS, the Examiner is invited to telephone the undersigned so duplicate copies can be provided immediately. Otherwise, Applicant requests that the Examiner please acknowledge consideration of these references by initialing a copy of the Form 1449 (in Exhibit A) and returning it with the next communication.

Applicant thanks the Examiner for acknowledging the supplemental IDS that was filed on July 23, 2003.

Applicant requests that the Examiner, in the next communication, please acknowledge receipt of the second supplemental IDS, which was mailed to the office on February 10, 2004, and acknowledged as received on February 13, 2004.

Finally, Applicant submits herewith a third supplemental IDS, and requests that the Examiner acknowledge receipt and consideration of the information provided therewith.

Rejections under 35 U.S.C. §103(a)

Claims 1-17 and 28-37 are rejected under 35 U.S.C. §103(a), as allegedly unpatentable over Yasui *et al.* (1990) in view of Kochel *et al.* (2002) and Ivy *et al.* (2000). Applicant traverses this rejection, and requests that it be withdrawn in light of the arguments presented below.

MPEP §706.02(j) states that, in order for an obviousness rejection to be proper, "the [cited] prior art reference (or references when combined) must teach or suggest all the claim limitations." In the current instance, the cited references, either alone or in combination, do not teach or suggest all of the limitations of the pending claims. In particular, none of the cited references, nor any combination thereof, teach or suggest "an isolated nucleic acid comprising a transcriptional unit encoding a signal sequence of a structural protein of a first flavivirus and an immunogenic flavivirus antigen of a second flavivirus," which language is copied directly from

the original and still pending Claim 1. All of the currently pending claims depend, directly or indirectly from Claim 1, and thus all include the features quoted above.

Applicant's currently claimed invention includes (1) a single nucleic acid that comprises a transcriptional unit encoding (2) a signal sequence of a structural protein of a **first** flavivirus and (3) an immunogenic flavivirus antigen of a **second** flavivirus. Thus, within the single nucleic acid molecule there is contained a transcriptional unit that contains sequences from **two, different flaviviruses**; one flavivirus provides a signal sequence, and the other flavivirus provides a sequence encoding an immunogenic flavivirus antigen. Such a chimeric nucleic acid is not taught, explicitly or implicitly, by any of the cited references, and the rejection under §103(a) is therefore improper. The deficiencies of each of the three cited references are discussed below.

Yasui *et al.* (*Southeast Asian J. Trop. Med. Public Health*, 21(4):663-669, 1990)

Yasui is cited for teaching that PrM and E proteins having signal sequences, which are required for expression. The Office action admits, however, that Yasui "does not disclose constructs encoding a signal sequence from a first flavivirus and a second flavivirus immunogen." Applicant does not dispute this failing of Yasui.

Kochel *et al.* (US 6,455,509)

Kochel is cited for teaching "preparation of nucleic acid dengue virus vaccines comprising a nucleic acid encoding the prM signal sequence and the envelope protein." It is further alleged in the Office action that "[t]hese genes may be from the same isolate or different isolates." Applicant contests this interpretation of Kochel, at least in so far as it appears to indicate that Kochel provides a single transcriptional unit comprising components from two different flaviviruses.

As a preliminary matter, Kochel discusses only dengue isolates. The Office action acknowledges, and Applicant agrees, that the reference therefore cannot and does not teach (explicitly or implicitly) any of Applicant's constructs that contain either a signal sequence or an immunogen encoding sequence from a non-dengue flavivirus.

In addition, Kochel does not teach a **single transcriptional unit** comprising components from two different dengue viruses (let alone a non-dengue flavivirus and a dengue virus). The teachings of Kochel are directed to "[e]ukaryotic plasmid expression vectors containing the PreM and at least part of the E gene of **a** virus selected from the group consisting of dengue-1 virus, dengue-2 virus, dengue-3 virus and dengue-4 virus . . . ." (Col. 3, lines 37-41) (emphasis added). These plasmids are alleged to be useful, alone or in combination with one another, as a DNA vaccine against dengue virus. The Kochel patent is explicit in stating that the plasmids contain "at least part of the E gene of **a** virus selected from" the specified dengue serotypes (see, *e.g.*, Col. 3 at line 39-40) (emphasis added).

To the extent that a vaccine containing sequences from more than one dengue virus is contemplated by Kochel, it is in the form of a multi-virus vaccine (directed to multiple viruses) that is a mixture of plasmids, each of which is specific for one serotype (see, *e.g.*, Col. 3 at lines 42-43; claims 2-4). For instance, at Col. 9, lines 36-39, the Kochel reference refers to a "tetravalent dengue DNA vaccine that provides protection against all four serotypes can be prepared by **combining the four different DNA vaccines** to form a tetravalent **mixture** . . ." (emphases added). The examples describe production of plasmids, each of which contain only sequences from a single dengue serotype. In addition, the claims in Kochel indicate that the inventors contemplate their invention as involving mixtures of different plasmids, with each plasmid containing "preM and at least 92% of the envelope gene of **a** dengue" virus selected from Den-1, Den-2, Den-3, and Den-4 (emphasis added). This explicitly indicates that both the preM sequence and the E sequence are from **the same** dengue virus.

The only place in Kochel that might be interpreted as indicating that a single plasmid might contain sequences from more than one dengue virus is at Col. 9, line 39-40, which states that a tetravalent dengue DNA vaccine can be prepared . . . "by cloning various combinations of the genes into one or more plasmid vectors." Even this passage, however, does not teach the inclusion, **within a single transcriptional unit**, of a signal sequence from a first flavivirus and an immunogen encoding sequence from a second flavivirus. At best, this passage of Kochel

might be seen to teach a plasmid that contains up to four different transcriptional units, each of which contains sequence from a single flavivirus.

Ivy *et al.* (US 6,136,561)

Ivy is cited for teaching "preparation of nucleic acid constructs comprising a first nucleotide sequence encoding a signal sequence and a second nucleotide sequence encoding the E antigen of any given flavivirus (*e.g.*, dengue, JEV, TBE, YFV, WNV, or SEV). The signal sequence may consist of either the $htPA_L$ leader sequence or the prM leader sequence." Applicants dispute this interpretation of Ivy, at least in so far as it appears to indicate that the reference teaches a single transcriptional unit comprising sequences from two different flaviviruses.

Ivy describes a construct encoding 60% or 80% envelope (E) protein from a flavivirus that can be expressed and secreted using one of very few specific leader sequences. The leader sequences provided by Ivy are the yeast α-mating factor prepropeptide leader sequence (preproMFα_L) (see Col. 7, lines 5-6), human tissue plasminogen activator secretion signal sequences for the propeptide (tPA_L) (see Col. 7, lines 8-9), or "**the homologous** premembrane (prM) leader" (see Col. 7, line 10; Col. 9, line 49) (emphasis added). Thus, the only flavivirus signal sequence that is suggested or taught by Ivy is the signal sequence from the same virus as that from which the E protein encoding sequence originates (**the homologous** leader).

Nowhere in Ivy is there provided a description of using a signal sequence (such as the prM leader) from a different flavivirus than the one that provides the portion of E protein encoded by the construct. It is apparent, when the Ivy patent is read as a whole, that the inventors contemplated only using sequences from a single virus, or an E protein fragment sequence from a virus and a signal sequence/leader from a non-virus organism (such as yeast or humans). The only examples of additional leaders proposed in Ivy are other non-viral sequences (see, *e.g.*, Col. 9, lines 49-54, which states "[o]ther secretion signal peptides or secretion leader pre/pro peptides, such as those associated with invertase or acid phosphatase of *S. cerevisiae* or with glucoamylase of *C. albicans* or of *A. niger* or the bovine chymosin prepropeptide secretion leader can also be used.") There is no indication anywhere in Ivy that the signal sequence/leader

of a different virus can or should be used. It required the current Applicant's teachings for one to consider such a construct, and such hindsight is impermissible.

Applicant further notes that Ivy is limited to constructs express only a **portion** of the E protein (*e.g.*, the B domain or 60% or 80% of the E protein). Thus, at the very least, Applicant's claims in which the immunogenic flavivirus antigen of the second virus includes the essentially complete E protein, the essentially complete prM/M protein, or both prM/M and E proteins (*e.g.*, claims 4-9) are distinguishable from the teachings in Ivy.

None of the references cited provide any explicit or implicit teaching to construct a single transcriptional unit including a signal sequence from a first flavivirus and an immunogen-encoding sequence from a second flavivirus. Lacking this, **the cited references do not teach all of the limitations of the pending claims and therefore they do not support a *prima facie* case of obviousness of the claimed invention**. Applicant requests that this rejection be withdrawn as to all of the pending claims.

CONCLUSION

It is respectfully submitted that the pending claims, without any amendment, are in a condition for allowance in light of the arguments presented above.

If any issues remain, the Examiner is formally requested to contact the undersigned attorney prior to issuance of the next Office action, in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. Applicant submits the foregoing Amendment so that the Examiner may fully evaluate Applicant's position, thereby enabling any such interview to be more focused.

This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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